

REMARKS

Claims 22-33 are under examination. Applicants thank Examiners Szperka and Ewoldt for the interview held with applicants' representative on November 14, 2006. The issues raised during the interview are discussed below.

Cross-Reference to Related Applications

Applicants have amended the specification to indicate that the present application claims benefit of U.S. Provisional Application Serial No. 60/261,405 filed on January 11, 2001. This application is also a continuation-in-part of U.S. Application Serial No. 10/030,522 filed December 31, 2001, which is the U.S. National Phase application of PCT/EP00/06677 filed July 13, 2000. PCT/EP00/06677, in turn, claims benefit of U.S. Provisional Application Serial No. 60/143,891, filed July 14, 1999 and GB 9916450.1 filed July 14, 1999. (A copy of applicants' priority claim as filed January 11, 2002 is attached as Appendix A.)

Claim Rejections under 35 U.S.C. § 112, first paragraph

All claims stand rejected under 35 U.S.C. § 112, first paragraph on enablement and written description grounds. For the following reasons, these rejections should be withdrawn.

As an initial matter, applicants note that claim 22 has been amended to relate to "A method for treating a mammal at risk of developing Systemic Inflammatory Response Syndrome or suffering from Systemic Inflammatory Response Syndrome..." Claim 22, as amended, reads:

22. A method for treating a mammal at risk of developing Systemic Inflammatory Response Syndrome or suffering from Systemic Inflammatory Response Syndrome by administering a partial inhibitor of factor VIII to the said mammal which is a monoclonal antibody against factor VIII or an antigen binding fragment of said monoclonal antibody, said antibody or fragment being able to recognize epitopes located in the C1 domain of factor VIII.

Support for the present amendment is found throughout the specification. For example, applicants point out that the specification at page 1 (lines 25-27) states; "Systemic inflammation is the possible endpoint of a number of clinical conditions including pancreatitis, ischemia, multiple trauma and tissue injury, haemorrhagic shock, immune-mediated organ injury and infection." The skilled artisan would recognize that such patients are at risk of developing SIRS and therefore would understand that such patients would benefit from prophylactic treatment according to the claimed method. Applicants, at page 24 (lines 1-3), further note that the methods of the invention are useful for "prophylactic or therapeutic treatment." No new matter has been added by the present amendment.

In connection with the enablement rejection, the Office asserts that the practice of the invention would require undue experimentation "to make the genus of antibodies recited in the instant claims" and that "prevention [of SIRS] requires the recited method to be completely effective in all patients at all times." For the following reasons, these grounds of rejection should be withdrawn.

With respect to the prevention issue, applicants note that this basis of the enablement rejection may be withdrawn in view of the present claim amendment which specifies that the method is directed to treating a patient at risk of developing SIRS or suffering from SIRS, an amendment suggested by the Office during the interview of November 14, 2006.

Turning to the enablement of the genus of antibodies recited in the instant claims, applicants again note that such antibodies or antigen-binding fragment of such monoclonal antibodies, which are partial inhibitors of factor VIII, are routinely produced absent undue experimentation. First, applicants again point out that, as detailed in the

application at Example 1 and Example 5 respectively under the headings "Production of Monoclonal Antibodies Derived from Hemophilia A Patients" and "Monoclonal Antibodies Derived from Hemophilia A Patients Partially Inhibit Thrombin Formation in vitro", Krix-1 was obtained by a cloning procedure which starts from B lymphocytes obtained from patients suffering from Hemophilia, more particularly from patients having an impaired factor VIII function. Such patients are then administered a sufficient amount of wild-type protein to elicit an immunological response, i.e. the production of antibodies directed against wild-type factor VIII. After isolation of the B lymphocytes from these patients, those cells producing antibodies with the desired properties are selected.

Indeed, applicants' specification at page 17 (line 34) through page 8 (line 14) teaches production of partial inhibitors:

'Human monoclonal antibodies of the desired specificity and characteristics are produced by transformation of B lymphocytes obtained from the peripheral blood of patients suffering from hemophilia A or acquired hemophilia. [...] In order to elicit a more specific immunological response, patients are sought who have an impaired function of a physiologically active protein, e.g. factor VIII. By "impaired" is meant that some residual function is available but that this is less than is known for the wild-type of the same protein. A comparison between the self-protein and the wild-type protein should exhibit a difference in the two proteins, preferably in a region or domain which is of interest. The difference may be a deletion or a substitution of one or more amino acids with others. The patients are then administered enough of the wild-type protein to elicit an immunological response. Then, B-lymphocytes are extracted from the patients and selected based on the production of antibodies which have desirable properties. Although reference is made to "patients" above, the method in accordance with this embodiment may be applied generally to mammals. The above procedure results in a greater chance of obtaining antibodies which target the domain containing the defect.'

Accordingly, applicants' specification teaches a method which specifically ensures the generation of partial inhibitory antibodies. Indeed, patients having a partially impaired

physiological function of factor VIII are described as patients in which some residual factor VIII activity is present, as a result of a mutation in the domain of interest (here the C1 domain). The mutation is one which does not completely inactivate factor VIII function. The fact that factor VIII is only partially impaired in most of these patients is because complete impairment of factor VIII function significantly reduces the survival rate. When the wild-type factor VIII protein is administered to these subjects, antibodies are generated within this patient against the corresponding wild-type epitope corresponding to this mutation (as this is recognized as 'foreign'). Similar to the effect of the presence of the mutation at this position in factor VIII, the antibodies directed against this epitope of factor VIII will result in only partial inhibition of factor VIII activity.

To further support applicants' position that obtaining antibodies from "Hemophilia A Patients" as described in the specification is a routine matter, applicants note that patients were known in the scientific literature to generate polyclonal antibodies capable of inhibiting factor VIII function. Indeed, it was described as early as 1982, that polyclonal antibodies inhibiting the co-factor activity of factor VIII can be classified as type I or type II inhibitors according to their capacity to inhibit factor VIII either completely (type I) or only partially (type II) (see, for example, Gawryl et al., Blood (1982) 60:1103; copy enclosed as Appendix B (see also Information Disclosure Statement initialed April 5, 2004; copy enclosed as Appendix C)). The present invention accordingly demonstrates that such partial inhibitory antibodies can be generated most particularly in patients in which the Hemophilia is a result of partial impairment of factor VIII activity due to a mutation in the C1 domain of factor VIII. Again, obtaining a partial inhibitory antibody of factor VIII cannot be considered undue experimentation.

Finally, in connection with the enablement rejection, applicants again direct the office's attention to the Declaration of Dr. Jean-Marie Saint-Remy filed October 20, 2005 (copy enclosed as Appendix D). Here Dr. Saint-Remy makes clear that the method as described in the application as filed could indeed be used to reproduce a partial inhibitor, using the production of the antibody termed "RHD5", as an example. More particularly paragraphs 11 and 12 of that declaration provide data that describe the method used for obtaining antibody RHD5, which corresponds to the method described

in the application. Under paragraphs 13 to 16, the partial inhibitory activity of this antibody and its ability to compete with Krix-1 is detailed. Such data indicate that antibodies falling within the scope of the claims are produced using routine methods and absent undue experimentation following the methods described in the application.

The Office further asserts that all of the claims are unpatentable under § 112, first paragraph, because they lack an adequate written description. Here, relying on the Federal Circuit's opinion in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) 19 F.3d 1559, the Office, in essence, asserts that because the specification discloses only one member of the genus of antibodies recited in the independent claim a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of antibodies at the time the application was filed. For the following reasons, this rejection should also be withdrawn.

Applicants again direct the Office's attention to the Gawryl reference which describes a class of factor VIII antibodies known in the scientific literature at the time the application was filed that do not completely inactivate factor VIII.

Applicants next submit that administration of "a partial inhibitor of factor VIII to the said mammal which is a monoclonal antibody against factor VIII or an antigen binding fragment of said monoclonal antibody, said antibody or fragment being able to recognize epitopes located in the C1 domain of factor VIII" as recited broadly in the invention would naturally occur to one skilled in the art reading the description. Applicants' description is clearly not limited to KR1X-1. Broader claim language, in this case, is permissible because the description of the use of a partial inhibitor of factor VIII throughout entire specification would immediately convey to any skilled person that applicant invented a method that involves administration of a partial inhibitor of factor VIII which binds to the C1 domain of factor VIII. The Gawryl reference provides additional evidence of the knowledge of one skilled in the art of anti-factor VIII, and as such supports applicants' position that to the ordinary skilled worker applicants' specification would be understood to include a class of antibodies that did not completely inactivate factor VIII as such partial inhibitors. Accordingly, under the facts of this case, applicants assert that, in view of the broad description of using partial

inhibitors of factor VIII that bind to the C1 domain and the results obtained using one such antibody, KRIX-1, and the fact that additional antibodies that did not completely inactivate factor VIII were known in the art, that the scope of the pending claims would be so readily recognized by one of ordinary skill in the art. Accordingly, on this basis alone, the written description rejection should be withdrawn.

Moreover, applicants note that, the Federal Circuit, in *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. May 26, 2006) has stated:

[I]t is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. See *Capon*, 418 F.3d at 1357 ("None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., *Regents v. Lilly*, *Fiers v. Revel*, *Amgen*, or *Enzo Biochem*, require a redescription of what was already known."). Thus, "[w]hen the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh." *Id.* at 1358. Rather, we explained that:

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

The court further stated (emphasis added):

Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention. As we stated in *Capon*, "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358. Indeed, the forced recitation of known sequences

in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference [note omitted] (where permitted) of such genes and sequences.

Applicants submit that the present specification provides a written description of the presently claimed invention in sufficient detail to satisfy the standard set by the Federal Circuit in *Falkner*, 448 F.3d 1357, 79 USPQ2d 1001. Like the situation in *Falkner*, where that the written description of a genus of poxvirus DNA was supported by mentioning vaccinia virus, a poxvirus, applicants' disclosure of the use of partial inhibitors of factor VIII and the description of the use of the KRIX-1 antibody or an antigen-binding fragment thereof supports the written description of the genus of partial inhibitors encompassed by the present claims.

In addition, applicants point out that claim 31 has been amended to require that the monoclonal antibody or fragment of the antibody that includes CDR regions in its variable heavy chain sequence with at least 95% sequence identity to the amino acid sequence of the CDRs depicted in figure 12 and/or includes CDR regions in its variable light chain sequence with at least 95% sequence identity to the amino acid sequence of the CDRs depicted in figure 13. Support for this amendment is found in the specification, for example, at page 13 (lines 15-18).

Finally, in connection with the assertion that "applicants' specification does not disclose the precise epitope recognized by the recited genus of antibodies, nor does it identify the structure an antibody must comprise in order to comprise the recited function", applicants note the following. Applicants point out that they are merely claiming a class of antibodies that recognize the C1 domain of factor VIII. Applicants also point out that the Office does not question that the C1 domain is a fully characterized antigen, in view of its structure, formula, chemical name, or its physical properties. Indeed, the USPTO Guidelines are persuasive authority for the proposition that a claim directed to "any antibody which is capable of binding to antigen X" would

have sufficient support in a written description that disclosed "*fully characterized* antigens." Synopsis of Application of Written Description Guidelines, at 60, *available at* <http://www.uspto.gov/web/menu/written.pdf> (last visited December 26, 2006) (emphasis added). Although the present claims are directed to methods of using antibodies that recognize the C1 domain of factor VIII, the same principles apply in the present situation, and on this basis too the written description rejection should be withdrawn.

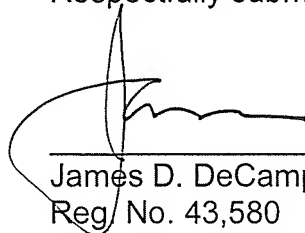
CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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